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ELI LILLY AND COMPANY

By KS Rhoades Date 4-24-03

#38

Dec.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Mark Brader, *et al.*	
Serial No.: 08/484,542	
Filed: June 7, 1995	Group Art Unit: 1631
For: **Stabilized, Acylated Insulin Formulations**	Examiner: M. Allen
Docket No.: X-10097	

REQUEST FOR INTERFERENCE UNDER 37 C.F.R. § 1.607

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants seek an interference between the present application and two unexpired patents.

I. Identification Of The Patents And Patent Applications [Rule 607(a)(1)]

Applicants seek to have an interference declared between the present application and U.S. patent nos. 5,750,497 ("the '497 patent") and 6,011,007 ("the '007 patent").

II. The Proposed Count [Rule 607(a)(2)]

Applicants propose that the count read in the alternative. The first recited alternative is identical to claim 28 of the

present application. The second recited alternative is identical to claim 1 of the '497 patent, except that the phrase "is deleted or" is inserted into part (c), such that "Xaa at position B30 is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys." The proposed count is as follows.

A composition comprising an aqueous solution of

(a) a fatty acid-acylated insulin or a fatty acid-acylated insulin analog in which the amino acid residue at position B30 is Thr, Ala or deleted, and

(b) zinc

OR

An insulin derivative having the following sequence:

```
                    S------------------S
A-Chain             |                  |
Gly-Ile-Val-Glu-Gln-Cys-Cys-Thr-Ser-Ile-Cys-Ser-
 1   2   3   4   5   6   7   8   9  10  11  12
                        |
                        S
                        S
B-Chain                 |
Xaa-Val-Xaa-Gln-His-Leu-Cys-Gly-Ser-His-Leu-Val-
 1   2   3   4   5   6   7   8   9  10   11  12

A-Chain (contd.)
Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Xaa
13  14  15  16  17  18  19  20  21
                            |
                            S
                            S
B-Chain (contd.)            |
    Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-
    13  14  15  16  17  18  19  20  21  22  23  24
```

B-Chain (contd.)
Phe-Tyr-Thr-Pro-Lys-Xaa
25 26 27 28 29 30

wherein

(a) Xaa at positions A21 and B3 are, independently, any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys;

(b) Xaa at position B1 is Phe or is deleted;

(c) Xaa at position B30 is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; and

(d) the ε-amino group of Lys^{B29} is substituted with an acyl group having at least 10 carbon atoms;

wherein the insulin derivative is a Zn^{2+} complex and the Zn^{2+} complex of the insulin derivative is more water soluble than the insulin derivative without Zn^{2+}.

III. Identification Of At Least One Claim In The Patents [Rule 607(a)(3)]

All of the claims in the '497 and '007 patents correspond substantially to both alternative recitals of the proposed count.

Pending application serial nos. 09/398,365 and 10/101,454 are continuing applications in the same family as the '497 and '007 patents. Applicants request that the Examiner review the claims in the pending continuing applications and determine whether at least one claim in each application corresponds to the proposed count.

IV. Presentation Of At Least One Claim In The Present Application [Rule 607(a)(4)]

Claim 28 of the present application corresponds exactly to the first alternative recited in the proposed count. Dependent claims 29-32, 57 and 61-66 correspond substantially

to the count, because they depend either directly or indirectly from claim 28.

Independent claim 27 corresponds substantially to the count, because claim 27 recites a composition comprising a fatty acid-acylated insulin or a fatty acid-acylated insulin analog in which the amino acid residue at position B30 is Thr, Ala or deleted, and zinc. Dependent claims 58, 60, 65 and 67 correspond substantially to the count, because they depend either directly or indirectly from claim 27.

V. Application Of Terms [Rule 607(a)(5)]

Support for the pending claims is found in the specification as shown in the following table.

Claim	Support In The Specification
27	Page 2, lines 26-27; page 4, line 7; page 5, lines 8-12; and the Abstract
28	Page 2, lines 26-27; page 4, line 7; page 5, lines 5-7; and the Abstract
29	Page 7, lines 23-26; and page 8, lines 8-10
30	Page 9, lines 19-20
31	Page 8, lines 18-21
32	Page 6, line 27; and claim 3 as originally filed
57	Page 8, lines 18-19; and page 9, line 14 to page 10, line 10
58	Page 7, lines 23-26; and page 8, lines 8-10
60	Page 6, line 27; and claim 3 as originally filed
61	Page 2, lines 20-21; page 4, line 21; and page 7, line 26
62	Page 8, lines 23-24
63	Page 8, line 27 to page 9, line 3
64	Page 8, lines 19, 20 and 28

65	Page 4, line 21
66	Page 4, line 21
67	Page 9, lines 19-20

VI. The Requirements Of 35 U.S.C. 135(b) Are Met [Rule 607(a)(6)]

Claim 28 was presented above in section IV as corresponding exactly to the first alternative recited in the proposed count.

The present application was filed on June 7, 1995, a date that is prior to the May 12, 1998 issue date of the '497 patent, and prior to the January 4, 2000 issue date of the '007 patent. When the present application was filed, it contained claim 1, directed to a storage stable insulin formulation comprising an aqueous solution of a fatty acid-acylated insulin and zinc, and claim 13, directed to a storage stable insulin formulation comprising an aqueous solution of a fatty acid-acylated insulin analog and zinc.

1. (as filed) A storage stable insulin formulation comprising an aqueous solution of a fatty acid-acylated insulin containing at least about 0.2 to about 0.7 mole of zinc per mole of said fatty acid-acylated insulin and having a pH of 6.8 to 7.8.

13. (as filed) A storage stable insulin formulation comprising an aqueous solution of a fatty acid-acylated insulin analog containing at least about 0.2 to about 0.7 mole of zinc per mole of said fatty acid-acylated insulin and having a pH of 6.8 to 7.8.

Claim 1 was amended in the amendment filed March 10, 1997. Claim 1 was canceled in the amendment filed August 19, 1998, and claims 27 and 28 were introduced. Thus, claims 27 and 28 were present less than one year prior to the May 12, 1998

issue date of the '497 patent, and were present prior to the January 4, 2000 issue date of the '007 patent.

Claim 13 was amended in the amendment filed March 10, 1997, and was canceled in the amendment filed on June 18, 1997. Thus, claim 13, which recited an analog, was present prior to the May 12, 1998 issue date of the '497 patent, and prior to the January 4, 2000 issue date of the '007 patent. Applicants reintroduce analog language into the claims in the amendment filed herewith.

Accordingly, the requirements of 35 U.S.C. 135(b) are met for claim 28, which corresponds exactly to an alternative recital of the proposed count, and are met for the remaining claims, which correspond substantially to an alternative recital of the proposed count.

VII. Evidence And Explanation Under 37 C.F.R. § 1.608(b)

Filed herewith is documentary evidence and an explanation of the evidence under 37 C.F.R. § 1.608(b) that demonstrate that Applicants' are *prima facie* entitled to a judgment relative to the patentee of the '497 and '007 patents.

Respectfully submitted,

Grant E. Reed
Attorney for Applicant
Registration No. 41,264
Phone: 317-276-1664

Eli Lilly and Company
Patent Division/GER
Lilly Corporate Center
Indianapolis, Indiana 46285

April 24, 2003

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Arlington, VA 22202, on the date appearing below.

ELI LILLY AND COMPANY

By KS Rhoades Date 4-24-03

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Mark Brader, *et al.*	)	
Serial No.: 08/484,542	)	
Filed: June 7, 1995	)	Group Art Unit: 1631
For: **Stabilized, Acylated Insulin Formulations**	)	Examiner: M. Allen
Docket No.: X-10097	)	

EXPLANATION OF EVIDENCE UNDER 37 C.F.R. § 1.608(b)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Following is an explanation under rule 608(b) that states with particularity the basis upon which Applicants are entitled to a judgment of priority relative to the effective filing date of U.S. patent no. 5,750,497 ("the '497 patent") and U.S. patent no. 6,011,007 ("the '007 patent").

I. The Request For Interference

In the request for interference filed herewith, Applicants seek to have an interference declared with the '497 and '007 patents, which are assigned to Novo Nordisk A/S ("the Patentee").

In the Request For Interference, Applicants propose that the count read in the alternative. The first recited alternative is identical to claim 28 of the present

application. The second recited alternative is identical to claim 1 of the '497 patent, except that the phrase "is deleted or" is inserted into part (c), such that "Xaa at position B30 is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys." The proposed count is as follows.

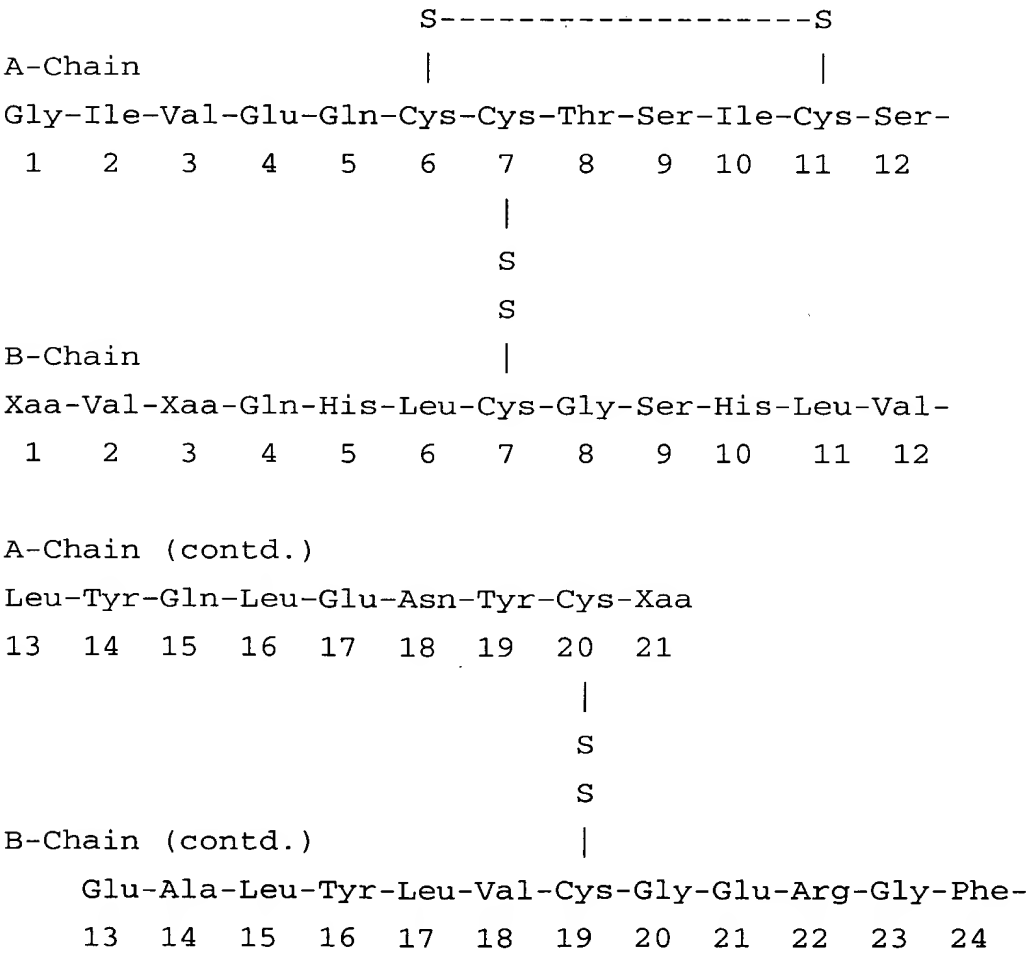
A composition comprising an aqueous solution of

(a) a fatty acid-acylated insulin or a fatty acid-acylated insulin analog in which the amino acid residue at position B30 is Thr, Ala or is deleted, and

(b) zinc

OR

An insulin derivative having the following sequence:



B-Chain (contd.)

Phe-Tyr-Thr-Pro-Lys-Xaa
25 26 27 28 29 30

wherein

(a) Xaa at positions A21 and B3 are, independently, any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys;

(b) Xaa at position B1 is Phe or is deleted;

(c) Xaa at position B30 is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; and

(d) the ε-amino group of Lys^{B29} is substituted with an acyl group having at least 10 carbon atoms;

wherein the insulin derivative is a Zn^{2+} complex and the Zn^{2+} complex of the insulin derivative is more water soluble than the insulin derivative without Zn^{2+}.

II. Evidence Under 37 C.F.R. § 1.608(b)

5 Declarations and 16 Exhibits which constitute documentary evidence are filed herewith. For the Examiner's benefit, following is a list of the Declarations and Exhibits.

Declaration by Dr. Mark Brader

Declaration by Mr. Michael Roy

Declaration by Mr. Richard A. Byrd

Declaration by Mr. Jonathan A. Klepfer

Declaration by Dr. Ahmed Deldar

Exhibit 1 Mark Brader Notebook 2685, pages 39-41

Exhibit 2 Mark Brader Notebook 2685, pages 47-48

Exhibit 3	Michael Roy Vacuum Dry Output
Exhibit 4	D06893 Study Plan
Exhibit 5	Clinical Pathology Interim Study Summary Report [9.24.1993]
Exhibit 6	Protocol Amendment No. 1
Exhibit 7	Clinical Pathology Interim Study Summary Report [9.28.1993]
Exhibit 8	Protocol Amendment No. 2
Exhibit 9	Clinical Pathology Interim Study Summary Report [10.4.1993, 10.6.1993]
Exhibit 10	Protocol Amendment No. 3
Exhibit 11	e-mail from Dean Clodfelter to Richard Byrd
Exhibit 12	e-mail from Richard Byrd to Mark Brader
Exhibit 13	Clinical Pathology Interim Study Summary Report [10.12.1993, 10.13.93]
Exhibit 14	Summary of Study D06893
Exhibit 15	1993 Calendar
Exhibit 16	D06893 Clinical Pathology Report

III. Explanation Of The Evidence Under 37 C.F.R. § 1.608(b)

A. Effective Filing Dates

The effective U.S. filing date of the present application is June 7, 1995.

The '497 and '007 patents claim priority benefit of abandoned U.S. application serial no. 08/190,829, filed February 2, 1994. Accordingly, February 2, 1994 is the earliest possible effective filing date for the '497 and '007 patents. The Danish priority filing date claimed is September 17, 1993.

B. Applicants Reduced To Practice First

Evidence filed herewith shows that Applicants reduced to practice a composition encompassed by each of the alternative recitals of the proposed count prior to September 17, 1993. Filed herewith is a Declaration by Dr. Mark Brader ("Brader Declaration"). Dr. Brader is a co-inventor in the present application, and an employee of Eli Lilly and Company, the assignee of the present application. Brader Declaration at ¶¶ 1 and 2.

Dr. Brader made his declaration in order to establish the dates of conception and reduction to practice of a composition comprising an aqueous solution of LY309132 and zinc. Brader Declaration at ¶ 3. LY309132 is a human insulin derivative that is acylated with a 16 carbon fatty acid (palmitic acid) at the epsilon amino group of lysine at position B29. Brader Declaration at ¶ 4. Dr. Brader refers to LY309132 as C16-insulin. *Id.*

Dr. Brader conceived of and made the composition described in his declaration on or before September 9, 1993. Exhibit 1 is a photocopy of pages 39 - 41 of his laboratory notebook and describes work he performed on September 8-10, 1993, to show the suitability of a C16-insulin zinc formulation for use in a clinical setting. Brader Declaration at ¶ 6.

In ¶ 7, Dr. Brader explains how he prepared lot DBF40Zn, which is C16-insulin with zinc. In ¶ 8, Dr. Brader explains that he wrote in page 40 of his notebook that the composition remained clear after the addition of zinc. In ¶ 8, he concludes that the presence of zinc did not appear to

adversely affect the solubility of C-16 insulin in the composition.

In ¶ 9, Dr. Brader explains that on September 9, 1993, he provided the composition described in ¶ 7 to Michael Roy for freeze drying, so that Dr. Brader could confirm that a lyophilized C16-insulin zinc formulation would dissolve adequately and that the C16-insulin would remain soluble upon reconstitution.

In ¶ 10, Dr. Brader explains that he received the lyophilized powder from Michel Roy on September 10, 1993, and he reconstituted the power by adding 1 mL of Humulin R diluent. Humulin R diluent is an aqueous solution. *Id.* In each of several aliquots of reconstituted C16-insulin with zinc, the C16-insulin dissolved completely in less than 30 seconds, yielding a clear solution. *Id.* The clarity of the reconstituted aqueous zinc containing solution and the short time needed for complete reconstitution confirmed the suitability of a lyophilized zinc powder for use in a clinical setting. Brader Declaration at ¶ 11.

Filed herewith is a Declaration by Mr. Michael Roy ("Roy Declaration"). Mr. Roy is an employee of Eli Lilly and Company, and he is not a co-inventor in the present application. Roy Declaration at ¶¶ 1 and 2. In ¶ 2 of his declaration, Mr. Roy explains that he received several solutions from Dr. Brader on September 9, 1993.

In ¶¶ 3-6, Mr. Roy explains how he freeze dried the samples, and that he provided the freeze dried samples to Dr. Brader on September 10, 1993. Mr. Roy refers to Exhibit 3 in his Declaration. Exhibit 3 is a photocopy of a chart tracing obtained during a freeze-drying procedure for the samples received from Dr. Brader. Roy Declaration at ¶ 3.

Included among the samples received by Mr. Roy was the DBF40Zn sample. *Id.* DBF40Zn is C16-insulin with zinc. Brader Declaration at ¶ 7.

In summary, the Brader and Roy Declarations, supported by Exhibits 1 and 3, establish corroborated conception of a

composition encompassed by the count on September 9, 1993. The Brader Declaration, supported by Exhibit 1, shows that Dr. Brader conceived of an aqueous solution containing an acylated insulin and zinc, embodied in lot DBF40Zn, and provided the composition to Mr. Roy for freeze drying on September 9, 1993.

Dr. Brader's conception is corroborated by the Roy Declaration, which is supported by Exhibit 3, which is a chart generated by Mr. Roy that documents that lot DBF40Zn was freeze dried on September 9, 1993.

The Brader and Roy Declarations, supported by Exhibits 1 and 3, also establish reduction to practice on September 9, 1993. Dr. Brader's observation in ¶ 10 of his Declaration that the C16-insulin solution remained clear after the addition of zinc meant that addition of zinc did not adversely affect the solubility of C16-insulin in the composition. As a result, the C16-insulin zinc solution would be expected to be absorbed when injected into an animal or human subject. Brader Declaration at 11. Since the aqueous insulin solution would be expected to be absorbed, it would be expected to exert a hypoglycemic effect *in vivo*. *Id.*

Collectively, the Brader and Roy Declarations, supported by Exhibits 1 and 3, establish conception and reduction to practice on or before September 9, 1993, which is prior to the Patentee's September 17, 1993 Danish filing date.

C. Applicants Conceived First, And Diligently Reduced To Practice

Even if it were concluded that Applicants did not reduce to practice first, evidence filed herewith establishes corroboration of conception of a composition that is encompassed by the proposed count on or before September 9, 1993. And other evidence filed herewith establishes that Applicants were diligent in reducing to practice from a time just prior to the Patentee's September 17, 1993 Danish priority application filing, until Applicants' own reduction to practice on October 13, 1993.

1. Evidence Establishes That Applicants Conceived First

The Brader and Roy declarations, supported by Exhibits 1 and 3, establish corroboration of conception of a composition that is encompassed by each alternative recital of the proposed count on or before September 9, 1993. Lot DBF40Zn, prepared by Dr. Brader and freeze dried by Mr. Roy, contained a 16 carbon fatty acid-acylated insulin and zinc.

2. Evidence Establishes Diligence Toward Reduction To Practice

Applicants began working toward a reduction to practice on a date prior to the Patentee's entry into the field. The Patentee's earliest possible effective foreign priority date is September 17, 1993. Accordingly, the earliest date on which the Patentee can assert entry into the field is *prima facie* September 17, 1993.

Applicants file herewith evidence of commencement of diligence toward a reduction to practice on September 16, 1993, one day prior to the Patentee's September 17, 1993 Danish priority application filing date. Applicants also file herewith evidence of diligence toward the reduction to practice, and the reduction to practice on October 13,1993.

Exhibit 15 is a 1993 calendar, and it will be referred to throughout this discussion.

Filed herewith is a declaration by Mr. Richard Byrd ("Byrd Declaration"), who is an employee of Eli Lilly and Company, and is not a co-inventor in this application. Byrd Declaration at ¶¶ 1 and 2. The work Mr. Byrd discusses in his declaration relates to work he did on behalf of the inventors on LY309132, which is C16-insulin. Byrd Declaration at ¶ 2. Mr. Byrd refers in ¶ 3 to Exhibit 4, which is a study plan for a dose ranging study with LY309132 in beagle dogs. The dose study number was D06893. *Id.* Mr. Byrd signed the document on September 16, 1993. *Id.* Thus, Exhibit 4 constitutes documentary evidence that diligence toward the a reduction to

practice occurred on September 16, 1993, which is one day prior to the Patentee's September 17, 1993 Danish priority application filing date.

In ¶ 4 of his declaration, Mr. Byrd explains that the study was to begin on September 22, 1993. In ¶ 4, Mr. Byrd further explains that reference standard lot RS0163 was to be used, that the first dose of LY309132 was to be 0.07 mg/kg animal weight, and that the compound was to be administered subcutaneously.

Mr. Byrd explains in ¶ 5 that Exhibit 4 sets forth that 3 male and 3 female animals would be used, and that each animal was identified by animal number. In ¶ 5, Mr. Byrd explains that the study plan provided for a "wash-out" period of several days between doses, in order for the each dose of LY309132 to be cleared from the animals before the next dose was given.

In ¶ 6, Mr. Byrd explains that blood glucose levels would be drawn from each animal.

September 18, 1993 was a Saturday, and September 19, 1993 was a Sunday. Exhibit 15.

In ¶ 7 of his declaration, Mr. Byrd explains that a 0.07 mg/kg dose of LY309132 was administered to each animal on September 22, 1993. From Exhibit 15, one sees that September 22, 1993 was a Wednesday.

Mr. Byrd also explains in ¶ 7 that Exhibit 5 is a photocopy of a Clinical Pathology Interim Study Summary Report by J.A. Klepfer, which sets forth the glucose and triglyceride levels for samples that were collected from all six animals at 0, 0.5, 1, 2, 4, 6 and 24 hours after the LY309132 was administered. Thus, the 24 hour time point occurred on September 23, 1993. Mr. Byrd explains in ¶ 7 of his declaration that the original report was printed on September 24, 1994.

September 25, 1993 was a Saturday, and September 26, 1993 was a Sunday. Exhibit 15.

Filed herewith is a declaration by Mr. Jonathan A.

Klepfer ("Klepfer Declaration"), who is an employee at Eli Lilly and Company, and is not a co-inventor in the present application. Klepfer Declaration at ¶¶ 1 and 2. In ¶ 2, Mr. Klepfer explains that the work he discusses in his declaration relates to work he did on LY309132, when he was part of a team that conducted dose ranging study D06893. In ¶ 4, Mr. Klepfer explains that Exhibit 5 is a photocopy of a Clinical Pathology Interim Study Report that he prepared and which was printed on September 24, 1993.

Referring again to The Byrd Declaration, in ¶ 8, Mr. Byrd explains that Exhibit 6 is a photocopy of Protocol Amendment no. 1, that the original document was printed on September 24, 1993, and was approved by him on the same date. He also explains in ¶ 8 that Exhibit 6 reflects that an appropriate blood glucose response was shown with the initial dose of 0.07 mg/kg LY309132, and that a second dose administration would be given to further define the hypoglycemic response. The study protocol was amended such that each animal would receive a 0.11 mg/kg dose of LY309132.

In ¶ 9, Mr. Byrd explains that a 0.11 mg/kg dose of LY309132 was administered to each animal on September 27, 1993. Mr. Byrd also explains in ¶ 9 that Exhibit 7 is a photocopy of a Clinical Pathology Interim Study Summary Report by J.A. Klepfer, which sets forth the glucose and triglyceride levels for samples that were collected from all six animals at 0, 0.5, 1, 2, 4, 6, 8 and 24 hours after the 0.11 mg/kg dose of LY309132 was administered. Thus, the 24 hour time point occurred on September 28, 1993. Mr. Byrd explains in ¶ 9 of Exhibit 16 that the original report was printed on September 28, 1993.

In ¶ 5 of his declaration, Mr. Klepfer explains that Exhibit 7 is a photocopy of a Clinical Pathology Interim Study Report that he prepared and which was printed on September 28, 1993.

Referring again to the Byrd Declaration, in ¶ 10, Mr. Byrd explains that Exhibit 8 is a photocopy of Protocol

Amendment no. 2, that the original document was printed on September 30, 1993, and was approved by him on the same date. He also explains in ¶ 10 that a third dose administration would be given to further define the hypoglycemic response. The study protocol was amended such that each animal would receive a 0.2 mg/kg dose of LY309132 on October 4, 1993. *Id.*

October 2, 1993 was a Saturday, and October 3, 1993 was a Sunday. Exhibit 15.

In ¶ 11 of his declaration, Mr. Byrd explains that a 0.2 mg/kg dose of LY309132 was administered to each animal on October 4, 1993. Mr. Byrd also explains in ¶ 11 that Exhibit 9 is a photocopy of a Clinical Pathology Interim Study Summary Report by J.A. Klepfer, which sets forth the glucose and triglyceride levels for samples that were collected from all six animals at 0, 0.5, 1, 2, 4, 6, 8 10 and 24 hours after the 0.2 mg/kg dose of LY309132 was administered. Thus, the 24 hour time point occurred on October 5, 1993. Mr. Byrd explains in ¶ 11 of his declaration that the original report was printed on October 4, 1993 for all time points except for the 24 hour time point, and the report for the 24 hour time point was printed on October 6, 1993.

In ¶ 6 of his declaration, Mr. Klepfer explains that Exhibit 9 is a photocopy of a Clinical Pathology Interim Study Report that he prepared and which was printed on October 4, 1993 for all time points except for the 24 hour time point, and the report for the 24 hour time point was printed on October 6, 1993.

October 9, 1993 was a Saturday, and October 10, 1993 was a Sunday. Exhibit 15.

Referring again to Mr. Byrd's declaration, in ¶ 12, Mr. Byrd explains that Exhibit 10 is a photocopy of Protocol Amendment no. 3, and that the original was printed on October 8, 1993 and approved by him on the same date. He also explains in ¶ 12 that Exhibit 10 reflects that Phase IV [the fourth dose] would be conducted using 0.2 mg/kg of LY309132 with zinc (lot 2685-47A, which contained 0.023 mg of zinc

oxide per vial).[1]

The LY309132 material was obtained from Dr. Brader. In his declaration, Dr. Brader explains in ¶¶ 13-14 that he made lot 2685-47A, which contained zinc, using C16-insulin lot 487EM3.

Referring again to Mr. Byrd's declaration, in ¶ 12, note 1, Mr. Byrd explains that Exhibit 11 is an e-mail message from Mr. Dean Clodfelter at Eli Lilly and Company, dated October 5, 1993, in which Mr. Clodfelter explains that lot 2685-47A was formulated with zinc, and that it was made from bulk lot 487EM3 by Dr. Brader. Mr. Byrd also explains that Exhibit 12 is an e-mail message from him to Dr. Brader, dated October 6, 1993, in which Mr. Byrd confirms receipt of zinc formulated C16-insulin.

In ¶ 13 of his declaration, Mr. Byrd explains that the 0.2 mg/kg dose of LY309132 with zinc was administered to each animal on October 11, 1993. Mr. Byrd also explains that Exhibit 13 is a photocopy of a Clinical Pathology Interim Study Summary Report by J.A. Klepfer, which sets forth the glucose and triglyceride levels for samples that were collected from all six animals at 0, 0.5, 1, 2, 4, 6, 8, 10 and 24 hours after the 0.2 mg/kg dose of LY309132 with zinc was administered. Thus, the 24 hour time point occurred on October 12, 1993. Mr. Byrd explains in ¶ 13 that the original report for all time points except for the 10 and 24 hour time points was printed on October 12, 1993, and that the report for the 10 and 24 hour time points was printed on October 13, 1993.

In ¶ 7 of his declaration, Mr. Klepfer explains that Exhibit 13 is a photocopy of a Clinical Pathology Interim Study Report that he prepared and which was printed on October 12 for all time points except for the 10 and 24 hour time

[1] Like lot DBF40Zn, lot 2685-47A contained a 16 carbon fatty acid-acylated insulin and zinc.

points, and on October 13, 1993 for the 10 and 24 hour time points.

Referring again to Mr. Byrd's declaration, in ¶ 14, Mr. Byrd explains that the data in Exhibit 13 show that the 0.2 mg/kg dose of LY309132 formulated with zinc exerted a hypoglycemic effect over time. Thus, reduction to practice occurred on October 13, 1993.

Exhibit 14 is a Summary of Study D06893 prepared by Mr. N.R. Bernhard on October 27, 1993. On information and belief, Mr. Bernhard is deceased, and thus cannot be relied upon to authenticate Exhibit 14. However, Mr. Byrd was copied on the document prepared by Mr. Bernhard. In ¶ 15 of his declaration, Mr. Byrd refers to Exhibit 14, and confirms that he received a copy of the Summary prepared by Mr. Bernhard. Mr. Byrd also explains that in Exhibit 14, the dates of administration of LY309132, and the dosages, are confirmed.[2]

In summary, the Brader, Byrd and Klepfer Declarations and Exhibits 2 and 4-15 filed herewith are documentary evidence that establish commencement of diligence on September 16, 1993, and diligence toward the reduction to practice on October 13, 1993.

Filed herewith is a declaration by Dr. Ahmed Deldar ("Deldar Declaration"). In ¶¶ 1 and 2 of his declaration, Dr. Ahmed Deldar explains that is an employee of Eli Lilly, and that he is not a co-inventor in the present application. Dr. Deldar refers to Exhibit 16, which is a photocopoy of the Clinical Pathology Report for dose ranging study D06893. In ¶ 3 of his declaration, Dr. Deldar explains that study D06893 related to LY309132, which is 16 carbon atom fatty acid-acylated insulin.

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[2] Applicants do not rely on the October 27, 1993 date of Exhibit 14 to show diligence, because the diligence period ended when reduction to practice occurred on October 13, 1993, which is the date on which the hypoglycemic effect of LY309132 formulated with zinc was seen. Exhibit 14 provides additional confirmation of the dates of administration of LY309132 during dose ranging study D06893.

In ¶ 5, Dr. Deldar explains that he discusses the administration of 0.7, 0.11 and 0.2 mg/kg doses of LY309132 in Exhibit 16. In ¶¶ 6-8, Dr. Deldar explains the hypoglycemic effect that was observed for the 0.7, 0.11 and 0.2 mg/kg doses of LY309132. In ¶ 9, Dr. Deldar explains that at page 2 of Exhibit 16, he noted that a 0.2 mg/kg dose of LY309132 containing zinc revealed relatively similar changes as he described for the 0.2 mg/kg does without zinc. He also explains that maximum effects on blood glucose level occurred following the administration of 0.2 mg/kg LY309132 with or without addition of zinc.[3]

IV. Conclusion

Documentary evidence filed herewith establishes that Applicants reduced to practice prior to the patentee. Alternatively, the documentary evidence filed herewith establishes that Applicants conceived prior to the Patentee, and were diligent in reducing to practice from September 16, 1993 (one day prior to the Patentee's September 17, 1993 Danish priority application filing date) to October 13, 1993, when Applicants' reduction to practice occurred.

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[3] In ¶ 10 of his declaration, Dr. Deldar explains that he signed his report on April 7, 1994. Applicants do not rely on the Deldar Declaration to show diligence, because the diligence period ended on October 13, 1993, which is the date on which the hypoglycemic effect of LY309132 formulated with zinc was seen. The Deldar Declaration and Exhibit 16 provide additional confirmation of that LY309132 formulated with zinc provided a hypoglycemic effect.

Accordingly, Applicants respectfully request that the Examiner acknowledge that Applicants are entitled to a *prima facie* judgment of priority of invention relative to the Patentee, and pass this application to the Board of Patent Appeals and Interferences for declaration of an interference.

Respectfully submitted,

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